Neurosurg Clin N Am 13 (2002) 355–370

NEUROSURGERY CLINICS OF NORTH AMERICA

Cerebral blood flow changes associated with intracerebral hemorrhage

Adnan I. Qureshi, MD*, Ricardo A. Hanel, MD, Jawad F. Kirmani, MD, Abutaher M. Yahia, MD, L. Nelson Hopkins, MD

Department of Neurosurgery and Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, 3 Gates Circle, Buffalo, NY 14209-1194, USA

The present article reviews the changes in cerebral blood flow (CBF) that occur in association with intracerebral hemorrhage (ICH) and the clinical implications of these changes, particularly in terms of blood pressure management, treatment of intracranial hypertension, and surgical evacuation. Data presented in the following sections are derived from laboratory studies and clinical reports.

Theoretic considerations

The role of CBF changes in the pathophysiology of ICH is not well understood, partly because the mechanism of neuronal damage is not fully understood [1]. Factors that are potentially responsible for these changes include (1) mechanical compression of surrounding microvasculature by the hematoma; (2) compromise of cerebral perfusion pressure (CPP) as a result of elevated intracranial pressure (ICP); (3) abnormalities in cerebral autoregulation as a result of vasoparalysis, which is attributed to acidosis, ischemia, and chronic hypertension; (4) release of vasoactive substances from the hematoma; and (5) release of vasoactive factors from inflammatory cells [2]. Secondary ischemic injury in regions surrounding and distant from the hematoma has been proposed as one of the mechanisms responsible for early neurologic deterioration and damage [1]. Recognition of a secondary ischemic insult is important because it may represent a potentially preventable form of neuronal injury [1]. Furthermore, the presence of ischemia would also suggest that pharmacologic treatment of hypertension in the acute period may actually be deleterious by precipitating ischemic injury [3]. Given the importance of this issue, considerable research has been directed recently toward furthering our understanding of CBF changes in ICH.

Laboratory studies evaluating cerebral blood flow in intracerebral hemorrhage

Changes in CBF have been studied in various animal models after the induction of ICH by different methods. The results of these studies [3–11] are summarized in Table 1. In most of the early laboratory investigations, an initial phase of hypoperfusion, presumably caused by compression of the adjacent microvasculature by the hematoma, was observed. A significant rise in ICP with a concomitant reduction in CPP at the time of hematoma induction was also observed. A reduction in regional CBF ($_{r}$CBF) is most prominent at that time, particularly in regions of the brain adjacent to the hematoma (caudate nucleus and overlying cortex), but it is re-established shortly [4,11]. This initial reduction in $_{r}$CBF apparently reflects immediate hemodynamic adjustments occurring in the

* Corresponding author.
E-mail address: aiqureshi@hotmail.com (A.I. Qureshi).

PII: S1042-3680(02)00012-8

Table 1
Summary of results of previous animal studies investigating cerebral blood flow changes after intracerebral hemorrhage

Study	Animals used	Anesthetic used	Hematoma induction	ICP changes	$_{r}$CBF measurement	Results
Ropper and Zervas 1982 [9]	Rat	Awake	0.24–0.28 mL of whole blood injected into the caudate nucleus over 1 second	—	H_2 clearance at intervals of 5–10 minutes for 1–7 hours after injection	Global reduction 23%–30% of baseline CBF; recovery of CBF associated with consciousness; no infarct*
Nath et al 1986 [6]	Rat	Halothane	25, 50, 100 μL of blood injected into the caudate nucleus over 2.5 minutes under 100 mm Hg of pressure	ICP rise proportional to hematoma volume; lowest mean CPP of 52 mm Hg	Quantitative autoradiography 1 minute after injection	$_{r}$CBF reduced in ipsilateral caudate and cortex proportional to volume of hematoma
Sinar et al 1987 [10]	Rat	Halothane	50-μL balloon inflated (intracerebral) over 2.5 seconds for 10 minutes and deflation	ICP rise with inflation and decline with deflation	H_2 clearance during inflation; quantitative autoradiography at 4 hours	$_{r}$CBF reduced in frontal cortex with inflation; CBF reduced in ipsilateral caudate at 4 hours, ischemic damage in caudate*
Nath et al 1987 [3]	Rat	Halothane	25 μL of blood injected in right caudate nucleus over 2.5 minutes	Early ICP rise followed by decline; CPP of 70–80 mm Hg	Quantitative autoradiography at 1 and 10 minutes and at 3 hours	$_{r}$CBF reduced in caudate and frontal cortex at 1 minute but not at 10 minutes or 3 hours, ischemic damage in cortex*

Kingman et al 1987 [5]	Rat	Halothane	50-μL balloon inflated (intracerebral) over 25 seconds for 2.5 minutes to 2.5 hours	—	Quantitative autoradiography at end of inflation	$_{r}$CBF reduced in ipsilateral basal ganglia and cortex proportional to duration of inflation; no difference after deflation
Bullock et al 1988 [4]	Monkey	Nitrous oxide	Uncontrolled amount of blood injected under arterial pressure into the caudate nucleus	Early ICP rise followed by decline; mean CPP of 56 mm Hg and 62 mm Hg at 10 minutes and 50 minutes, respectively	H_2 clearance at 10, 50, 90, 120, 150, and 180 minutes	$_{r}$CBF reduced in all regions at 10 and 50 minutes, most prominent in ipsilateral caudate and white matter
Nehls et al 1988 [7]	Rat	Halothane, nitrous oxide	50-μL balloon inflated (intracerebral) over 20 seconds for 5 minutes or 4 hours	—	Quantitative autoradiography at end of inflation period (5 minutes or 4 hours)	$_{r}$CBF reduced in ipsilateral caudate, more prominent after 4 hours of inflation
Nehls et al 1990 [8]	Rat	Halothane	50-μL balloon inflated (intracerebral) over 20 seconds for 5 minutes or 24 hours	—	Quantitative autoradiography at 24 hours	$_{r}$CBF reduced in ipsilateral cortex and caudate nucleus after 24 hours of inflation; ischemic damage in all animals*
Yang et al 1994 [11]	Rat	Nitrous oxide	100 μL of blood injected into right caudate nucleus over 5 minutes	—	Indicator fraction at 1, 4, 24, and 48 hours	$_{r}$CBF reduced globally at 1 hour, normalized at 4 hours, and reduced at 24 and 48 hours

CPP = cerebral perfusion pressure; ICH = intracerebral hemorrhage; ICP = intracranial pressure; $_{r}$CBF = regional cerebral blood flow; — = not measured.

From Qureshi AI, Wilson DA, Hanley DF, Traystman RJ. No evidence for an ischemic penumbra in massive experimental intracerebral hemorrhage. Neurology 1999;52:266–72; with permission.

* Histopathologic evaluation.

brain after ICH. Nath et al [3] observed that ischemia after ICH persisted only to a marginal degree beyond 10 minutes and that CBF returned to baseline values within 3 hours. Similarly, Yang et al [11] found a 50% reduction in CBF after ICH that returned to control values within 4 hours. Ropper and Zervas [9] observed a minor reduction in CBF (lowest rate in the range of 25–30 mL per 100 g/min) after injecting 0.24 to 0.28 mL of blood in the rat caudate nucleus to induce ICH. These reduced values were transient and returned to baseline within 4 hours. In the early studies, hemorrhage was induced by rapid bolus injection of blood or expansion of a microballoon in the brain parenchyma. Recent clinical studies suggest that the occurrence of an ICH is not a monophasic event [12,13]. The hematoma expands over time, allowing spatial and temporal compensatory responses that have not been reproduced by previous models.

We designed a new model of ICH in dogs to simulate the multiple phases of intracerebral hematoma in human beings [14]. Using this model, we performed a set of experiments to determine the effect of massive ICH on $_{r}$CBF and to test the hypothesis that ischemia persists in the perihematoma region after ICH. ICH was induced in each of eight anesthetized mongrel dogs by injecting autologous blood under arterial pressure in the deep white matter adjacent to the left basal ganglia. The volume of blood (7.5 mL) injected in the canine brain was equivalent to a 75-cm^3 hematoma in a human brain. Serial measurements of $_{r}$CBF were obtained using radiolabeled microspheres injected in regions around and distant from the hematoma. Measurements of cerebral oxygen extraction, cerebral metabolic rate of oxygen consumption ($CMRO_2$), cerebral glucose utilization, and lactate production were obtained by serial sampling of cerebral venous blood from the sagittal sinus. Mean arterial pressure and ICP were monitored continuously. We were unable to detect any changes in either $_{r}$CBF or the indices representing cerebral metabolism during the first 5 hours after ICH introduction. No differences were observed in $_{r}$CBF in gray and white matter in regions around and distant from the ICH at five different time points throughout the observation period. A threefold progressive rise in ICP was seen after ICH, however, along with a modest rise in systemic blood pressure. Despite observing characteristic changes in ICP and systemic blood pressure after ICH, no evidence of persistent cerebral ischemia was found. We did not study changes in $_{r}$CBF within the first few minutes after hematoma formation, because therapeutic decisions (ie, blood pressure management, surgical evacuation of a hematoma) have traditionally been based on the presence of a persistent ischemic penumbra after ICH.

Recent animal studies support our observations regarding the lack of a persistent region of ischemia in the perihematoma region. Wagner et al [15] studied the concentrations of different metabolites in the perihematoma region in pigs after inducing ICH by slow infusion of blood (similar to our experimental method). They concluded that blood flow changes in the perihematoma region are unlikely to be severe or prolonged on the basis of findings of unchanged ATP levels and increased phosphocreatine levels in the early hours after ICH. Another set of experiments demonstrated the lack of a protective effect of *N*-methyl-D-aspartate blockade on cerebral edema after ICH supporting the absence of ischemia in the pathogenesis of neuronal injury [16].

We think that the lack of any severe ischemia or prolonged reduction in $_{r}$CBF in the perihematoma region during the acute period after hemorrhage in recent experimental models is attributable to mechanical resistance and collateral supply of the cerebral tissue containing the hematoma. First, the mechanical compression induced by clot injection is incomplete in contrast to that induced by microballoon inflation. This premise is supported by the presence of $_{r}$CBF within the clot matrix in our study [14]. Furthermore, breakdown of the blood–brain barrier does not occur immediately after hematoma formation [3,11], which would be expected if there was significant mechanical distention or disruption of the interface between the pia mater and the vascular infrastructure. Second, abundant collateral supply from pial vessels arising from the middle cerebral artery compensates for any ischemia in the deep white matter and should be unaffected by the localized hematoma [14]. Mutlu et al [17] proposed a similar explanation for the preservation of gray matter in the perihematoma region in humans after hypertensive ICH. They attributed this finding to the abundant collateral supply provided by vertically penetrating cortical arterioles and to the mechanical resistance afforded by the dense tangential structure of white matter fibers to the expanding hematoma. In addition, the presence of elevated systemic blood pressure leads to high CPP, which may provide further protection against ischemia. On the basis of the more recent investigations conducted in experimental models, we hypothesize that incom-

plete mechanical compression, intact autoregulation, collateral circulation, and high CPP (as a result of systemic hypertension) prevent the occurrence of significant $_r$CBF changes in the perihematoma region.

Clinical studies evaluating cerebral blood flow in intracerebral hemorrhage

Numerous methods have been used to assess CBF in patients with ICH. They include Xenon-CT (Xe-CT), contrast-enhanced Xe-CT, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) [2,18–26]. A summary of clinical studies evaluating changes in CBF after ICH is provided in Table 2.

In all studies in which the Xe-CT method was used, hypoperfusion of the hemisphere ipsilateral to the hematoma was found [20,21,25,27,28]. By using this method, Suzuki et al [25] found a global reduction in CBF after putaminal hemorrhage, with more marked reduction in CBF in the hemisphere ipsilateral to the hematoma. In addition to hypoperfusion, hyperperfusion has been identified in areas surrounding the hematoma (''luxury perfusion'') in the subacute period of ICH through the use of Xe-CT. Miyazawa et al [21] reported focal hyperperfusion in 24 (23.5%) of 102 patients evaluated within 1 week of ICH onset. Patients who developed hyperperfusion were younger and more likely to be men. Hematoma volume was not a contributing factor. In an accompanying review of the literature, Miyazawa et al [21] found that hyperperfusion was reported to occur between 1 and 15 days after ICH onset.

Mayer et al [2] performed paired consecutive CT and ^{99m}Tc-hexamethyl-propylene amine oxime SPECT scans during the acute (mean = 18 hours) and subacute (mean = 72 hours) phases of ICH in 23 patients. Hypoperfusion was observed in the perihematoma region during the acute phase of ICA (Fig. 1). Follow-up SPECT scans in the subacute period documented improvement in $_r$CBF around the hematoma, although regions of hypoperfusion were present (Fig. 2). The mean ICH volume (18 mL) did not change; whereas the mean edema volume increased by 36% and the mean $_r$CBF deficit decreased by 55% between the acute and subacute phases. Edema volume on the second CT scan correlated positively with $_r$CBF deficit on the first SPECT scan and with the volume of reperfused perilesional tissue. The investigators observed that perilesional blood flow normalizes from initially depressed levels as edema forms during the first 72 hours after ICH and that the volume of edema eventually correlates with that of the reperfused tissue. These results suggest that the potential for perilesional hypoperfusion is highest in the earliest hours after ICH onset and implicate reperfusion injury in the pathogenesis of perihematoma edema formation. Rousseaux et al [23] studied the cerebral distribution by hexamethyl-propylene amine oxime SPECT mapping in 20 patients with ICH at varying intervals ranging from 1 to 95 days. Reduced tracer activity suggestive of hypoperfusion was a consistent finding in the ipsilateral cortex. Remote effects, such as reduction in $_r$CBF (functional diaschisis), were observed in the adjacent cortex (19 cases) and frontal cortex (14 cases) and in the contralateral cerebellum (16 cases). In the chronic phase, reduced perfusion was observed at the site of the resolved hematoma because of the presence of nonviable tissue.

Carhuapoma et al [29] reported the results of diffusion-weighted imaging and proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) in patients with ICH. Apparent diffusion coefficient (ADC) and lactate spectra values in perihematoma brain tissue were recorded and analyzed (an increase in ADC is consistent with vasogenic edema, and an increase in lactate spectra is suggestive of ischemia). Nine patients (mean age = 63.4 years, range: 36–87 years) were included in the study. Mean time from symptom onset to initial ^{1}H-MRSI was 3.4 days (range: 1–9 days), and mean hematoma volume was 35.4 cm^3 (range: 5–80 cm^3). Perihematoma diffusion values were obtained in all patients, and ^{1}H-MRSI measurements were obtained in five patients. The ADC was significantly higher in perihematoma regions than in contralateral corresponding regions of interest (consistent with vasogenic edema). Lactate surrounded the hematoma in two patients (suggestive of ischemia). Most patients with regions of vasogenic edema did not have metabolic changes consistent with ischemia. This preliminary data were inconsistent with ischemia as the primary mechanism for perihematoma tissue injury.

Kidwell et al [30] performed diffusion-perfusion MRI in 12 patients who presented with ICH. Imaging studies were performed within 6 hours of symptom onset in all patients. Perfusion mapping was obtainable in 6 patients, and ipsilateral hypoperfusion was documented in 5 of these patients. On diffusion-weighted imaging, reduced ADC values were observed in 3 of 12 patients. The significance of reduced ADC was not clear.

Table 2
Summary of results of previous clinical studies investigating cerebral blood flow changes after intracerebral hemorrhage

Study	Number of patients	Location of ICH	Interval from onset to examination	$_{r}$CBF measurement	Findings
Kawakami et al 1974 [27]*	44	Lateral (35) Mesial (9)	Within 3 weeks	Xe-CT	$_{r}$CBF decreased with a direct relation to level of consciousness
Kitahara et al 1996 [20]	22: 11 ICH, 11 control	Putamen	Preoperative (4), early postoperative (4), 1 week (5), 2–3 weeks (4), >4 weeks (11) (some patients had multiple scans)	Xe-CT	$_{r}$CBF of affected cerebral hemisphere and thalamus with the control group; rCBF of cerebral hemisphere increased transiently after surgical evacuation of hematoma
Miyazawa et al 1998 [21]	165	Putamen (88) Thalamus (37) Subcortex (27) Cerebellum (9) Brain stem (4)	Acute [within 1 week] (102) Subacute [1 week–1 month] (19) Chronic [>1 month] (44)	Xe-CT	Relative focal hyperperfusion identified in 24 (23.5%) of 102 patients with acute stage ICH; relative focal hyperperfusion appeared in the acute stage and did not persist for >30 days
Tanizaki 1988 [28]	13 (surgically treated)	Putamen	Preoperative and within 7 days of surgical evacuation	^{133}Xe and SPECT	Postoperative $_{r}$CBF improved in two thirds of cases even though operated in the subacute stage
Rousseaux et al 1991 [23]	20	Subcortex (8) Putamen (5) Thalamus (7)	1–95 days (33.2 ± 23.6 days)	SPECT	Hypoperfusion of ipsilateral cortex in 19 of 20 patients; contralateral cerebellar hypoactivity in 16 of 19 patients
Mayer et al 1998 [2]	23	Putamen (12) Thalamus (6) Gangliothalamic (2) Lobar (3)	Within 24 hours, repeated between 48 and 72 hours	SPECT	Flow deficit volumes observed in the initial scan with a 55% decrease on repeat scan; edema volume on the second CT scan correlated with flow deficit volume on initial scan; 4 patients had delayed cortical hyperperfusion
Siddique et al 2000 [24]	13: 4 surgical, 9 conservative management	Not described	Within 48 hours, repeat scan between 4 and 7 days	SPECT	Perfusion of affected hemisphere improved between the first and second examinations in all surgically treated patients; in the conservatively managed group, perfusion was worse in 6 patients, the same in 1, and slightly better in 2

Carhuapoma et al 2000 [29]	9	Basal ganglia (5) Lobar (3) Thalamus (1)	1–9 days (mean 3.4 days)	DWI ^{1}H-MRSI	Presence of vasogenic edema around the clot instead of recent cerebral ischemia
Kidwell et al 2001 [30]	12	Thalamus (4) Putamen (5) Lobar (3)	Median time of 2 hours (range: 47 minutes–5 hours)	Diffusion-perfusion MRI	Ipsilateral hemisphere hypoperfusion in 5 of 6 patients in whom perfusion map could be obtained; rim of decreased apparent diffusion coefficient in perihematoma region observed in 3 of 12 patients (unclear significance)
Uemura et al 1986 [31]	21	Thalamus (14) Putamen (3) Subcortical (4)	PET within 10 days (13) PET 11–30 days (12) PET 30 days after ICH (8) (some patients had multiple scans)	PET (^{15}O-water)	Marked decrease of $_{r}$CBF and $CMRO_2$ in a narrow zone around the hematoma; luxury perfusion in 2 cases (9.1%); diffuse reduction of CBF and $CMRO_2$ in affected and contralateral hemispheres
Diringer et al 1998 [18]	12	Thalamus (8) Basal ganglia (4)	17.8 ± 10.2 hours	PET (bolus water)	CBF symmetrically reduced in thalamic and ganglionic ICH
Hirano et al 1999 [19]	14: 6 ICH, 8 control	Thalamus (2) Putamen (2) Lobar (2)	Within 48 hours	PET (^{18}F-FMISO)	No areas consistent with hypoxia detected by ^{18}F-FMISO PET in patients with ICH
Zazulia et al 2001 [26]	19	Putamen (7) Thalamus (5) Lobar (7)	5–22 hours (15.4 ± 4.8 hours)	PET (^{15}O-water)	CBF and $CMRO_2$ reduced in periclot area compared with contralateral side; oxygen extraction fraction significantly less around the clot than within the hemisphere; hypoperfusion without ischemia surrounding ICH

CBF = cerebral blood flow; $_{r}$CBF = regional cerebral blood flow; $CMRO_2$ = cerebral oxygen metabolic rate; DWI = diffusion-weighted imaging; ^{18}F-FMISO = ^{18}F-fluoromisonidazole; ^{1}H-MRS = proton magnetic resonance spectroscopic imaging; ICH = intracerebral hemorrhage; SPECT = single-photon emission CT; Xe = xenon; PET = positron emission tomography.

* Pre-CT era study. Lateral and mesial types of hemorrhages related to location of lenticulostriate arteries.

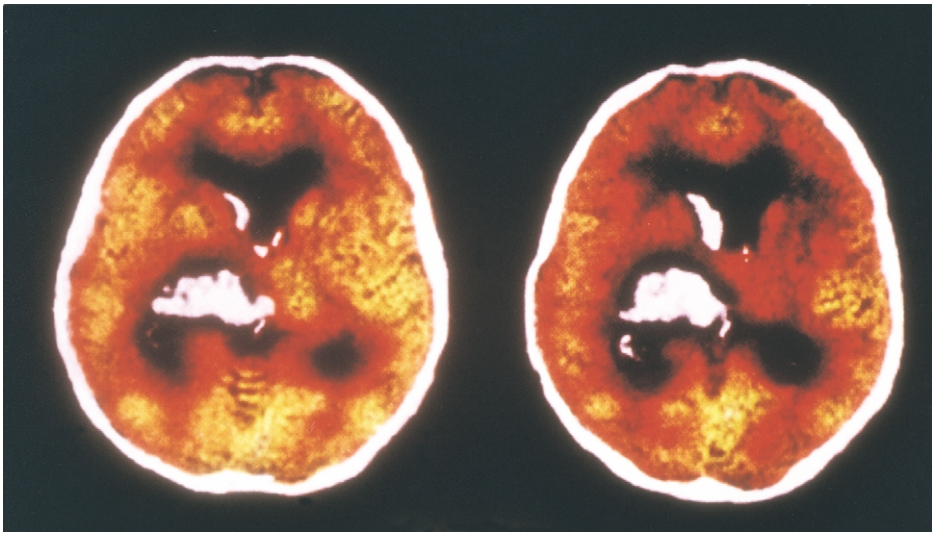

Fig. 1. Overlay of 2-hour CT and 4-hour single-photon emission CT (SPECT) images of a 69-year-old woman with typical SPECT findings after a 12-mL right thalamic hemorrhage. The images demonstrate a large region of hypoperfusion surrounding the hematoma. (*From* Mayer SA, Lignelli A, Fink ME, Kessler DB, Thomas CE, Swarup R, et al. Perilesional blood flow and edema formation in acute intracerebral hemorrhage: a SPECT study. Stroke 1998;29:1975; with permission.)

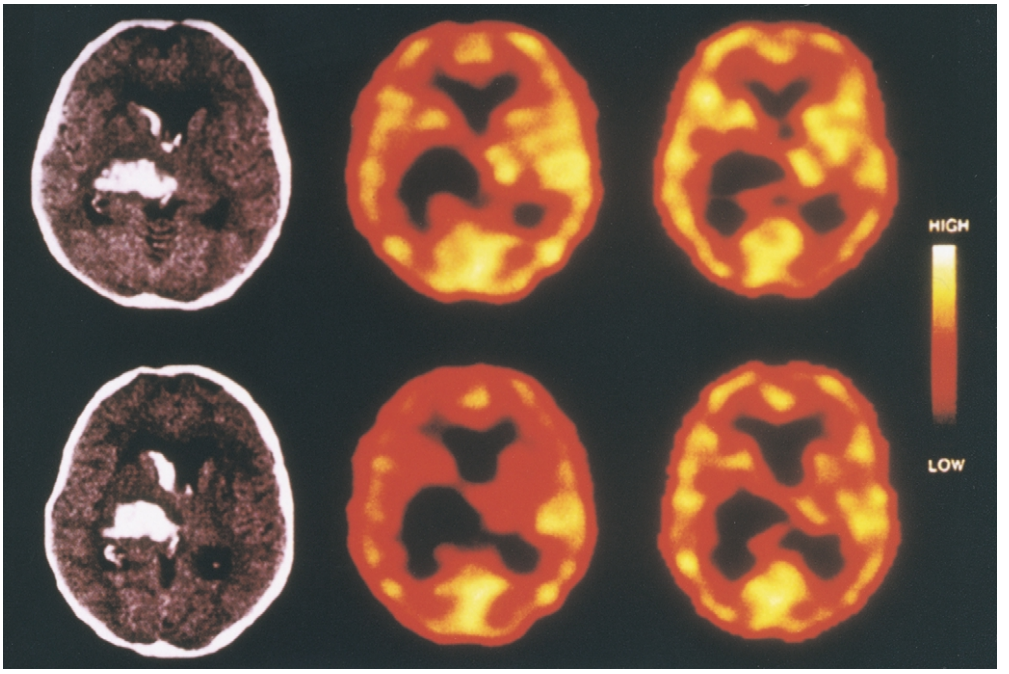

Fig. 2. Serial single-photon emission CT images show improving perihematoma blood flow from the acute to subacute periods (left, 2 hours; middle, 4 hours; right, 54 hours). The CT appearance of thalamic intracerebral hemorrhage is shown on the left. Cerebral blood flow (CBF) in the corresponding section in the acute phase is shown in the center. In the subacute scan (right), regional CBF has improved, although regions of hypoperfusion can be identified. (*From* Mayer SA, Lignelli A, Fink ME, Kessler DB, Thomas CE, Swarup R, et al. Perilesional blood flow and edema formation in acute intracerebral hemorrhage: a SPECT study. Stroke 1998;29:1975; with permission.)

Reduced ADC can be observed in regions under metabolic stress, which is consistent with ischemia, cytotoxic edema, and/or neuronal injury. The reduced ADC was observed in only a few patients, and the absence of moderate to severe hypoperfusion in the perihematoma region argued against a role of cerebral ischemia in hyperacute ICH.

Hypoperfusion of the ipsilateral hemisphere in patients with ICH has been documented by use of Xe-CT and SPECT scans in previous studies; however, an important determinant of associated consequences is the metabolic activity of affected tissue. Assessment of metabolic activity has been made possible with the availability of PET. Reductions in CBF and $CMRO_2$ in affected and contralateral cerebral hemispheres have been shown by use of PET scanning in ICH [18,31]. Uemura et al [31] measured $_rCBF$, oxygen extraction fraction, and $CMRO_2$ in 21 patients with hypertensive ICH using PET. They observed a localized decrease in CBF and $CMRO_2$ around the hematoma. Two cases were found to have distinct luxury perfusion around the hematoma. Zazulia et al [26] measured $_rCBF$, $CMRO_2$, and oxygen extraction fraction with PET in 19 patients 5 to 22 hours after hemorrhage onset. Measurements were determined in a 1-cm border around the clot. In 16 of the patients who had PET images that did not show any midline shift of the ventricles, mirror image measurements were obtained from contralateral regions. All measurements were corrected to allow for the volume occupied by the clot and the ventricles. Periclot $_rCBF$ and $CMRO_2$ values were significantly less than contralateral values (Fig. 3). Periclot oxygen extraction fraction was less than both hemispheric oxygen extraction fraction and contralateral regional oxygen extraction fraction. The reduction in oxygen extraction fraction around the clot was consistent with reduced metabolic demand and not cerebral ischemia. Therefore, no evidence was found for ischemia in the periclot zone of hypoperfusion in patients with ICH studied 5 to 22 hours after hemorrhage onset. Hirano et al [19] studied 6 patients at 24 and 43 hours (mean = 32 hours) after ICH and eight controls using PET with ^{18}F-fluoromisonidazole (^{18}F-FMISO) tracer to determine whether a zone of tissue hypoxia, possibly representing "penumbral" tissue, exists around an ICH. The ^{18}F-FMISO tracer is trapped within hypoxic but viable tissue that is likely to represent an ischemic penumbra. Four patients experienced deep (thalamic or basal ganglionic) hemorrhages and 2 experienced subcortical hemorrhages ranging in size from 5 to 70 cm^3. ^{18}F-FMISO PET did not detect any areas of increased tracer activity consistent with tissue hypoxia in patients with ICH. PET studies in the eight controls were also negative for any areas of increased tracer activity.

Summary of cerebral blood flow changes in intracerebral hemorrhage

On the basis of laboratory and clinical evidence, the changes in CBF associated with ICH can be summarized in three phases (Fig. 4).

Hibernation phase

During the acute period of ICH (within 48 hours of onset), a region of hypoperfusion develops predominantly in the periphery of the hematoma and, to a variable extent, within the ipsilateral hemisphere. A concomitant reduction in cerebral metabolism is observed in these areas. Initial evidence suggests that the reduction in cerebral metabolism exceeds that in CBF. Therefore, there is a decrease in the amount of oxygen required by and subsequently extracted from the affected cerebral tissue. The cerebral tissue is not ischemic because of the observed decrease in metabolism. This phenomenon can be referred to as a "hibernation phase" because of the combined state of hypoperfusion and hypometabolism that exists predominantly in regions surrounding the hematoma with variable extension beyond the periphery and occasionally into the contralateral hemisphere.

Reperfusion phase

The reperfusion phase of CBF starts approximately 48 hours after the onset of ICH. The pattern of CBF restoration is heterogeneous, and evidence of abnormality is still evident. Three different patterns of subacute blood flow are recognized: continued hypoperfusion, improved perfusion, and hyperperfusion. Increased perfusion at rates approaching normal values is evident in regions that initially demonstrated hypoperfusion. There is an accompanying increase in (recovery of) metabolic activity in previously hypometabolic regions. Improvement in $_rCBF$ in some regions may be delayed because of secondary insults, such as expansion of the hematoma. Hyperperfusion is a focal phenomenon and is attributed to local acidosis, inflammation, and impaired

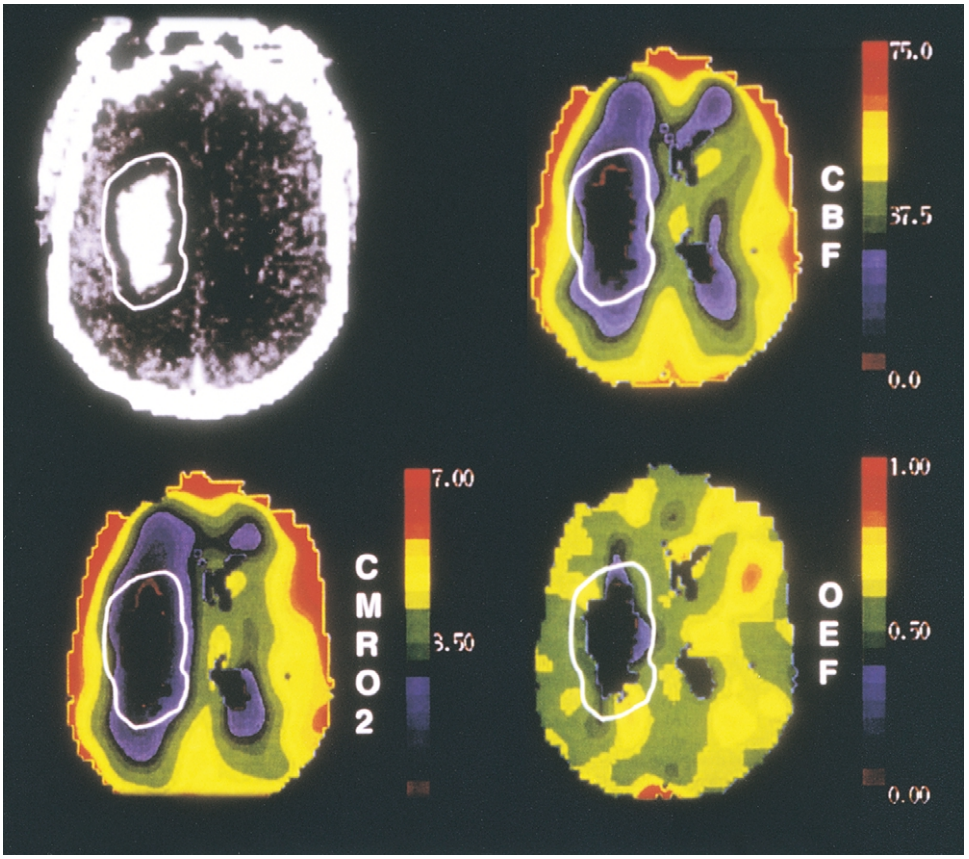

Fig. 3. Coregistered CT and positron emission tomography images of a 44-year-old hypertensive man with a left putaminal hemorrhage studied 21 hours after onset. The 1-cm wide periclot region was outlined in white on the CT scan and superimposed on the cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) images. Periclot flow, metabolism, and oxygen extraction fraction are all reduced compared with the contralateral hemisphere. The image on the lower right illustrates the decrease in cerebral metabolism occurring concomitantly, with hypoperfusion preventing ischemia. (*From* Zazulia AR, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. J Cereb Blood Flow Metab 2001;21:806; with permission.)

autoregulation in relatively intact regions of surrounding neuronal tissue.

Normalization phase

After approximately 14 days, CBF approaches normal values, assuming a more homogeneous pattern. Imaging performed after 30 days has not shown abnormalities in $_{r}$CBF. Normalization is attributed to resolution of the hematoma and its mass effect. Another factor that contributes to restoration of flow is neovascularization in peripheral regions of neurogliotic tissue. Flow deficits observed within the matrix of the hematoma are consistent with nonviable tissue.

Clinical implications of cerebral blood flow changes in intracerebral hemorrhage

CBF changes are frequently observed in patients with ICH. Therefore, it is important to understand factors that influence CBF and, subsequently, clinical outcome.

Effect of blood pressure treatment on cerebral blood flow in intracerebral hemorrhage

Elevated blood pressure is common after ICH and is associated with hematoma expansion and poor outcome [32]. It remains unclear whether elevated blood pressure predisposes patients to expansion of the hematoma or is a consequence

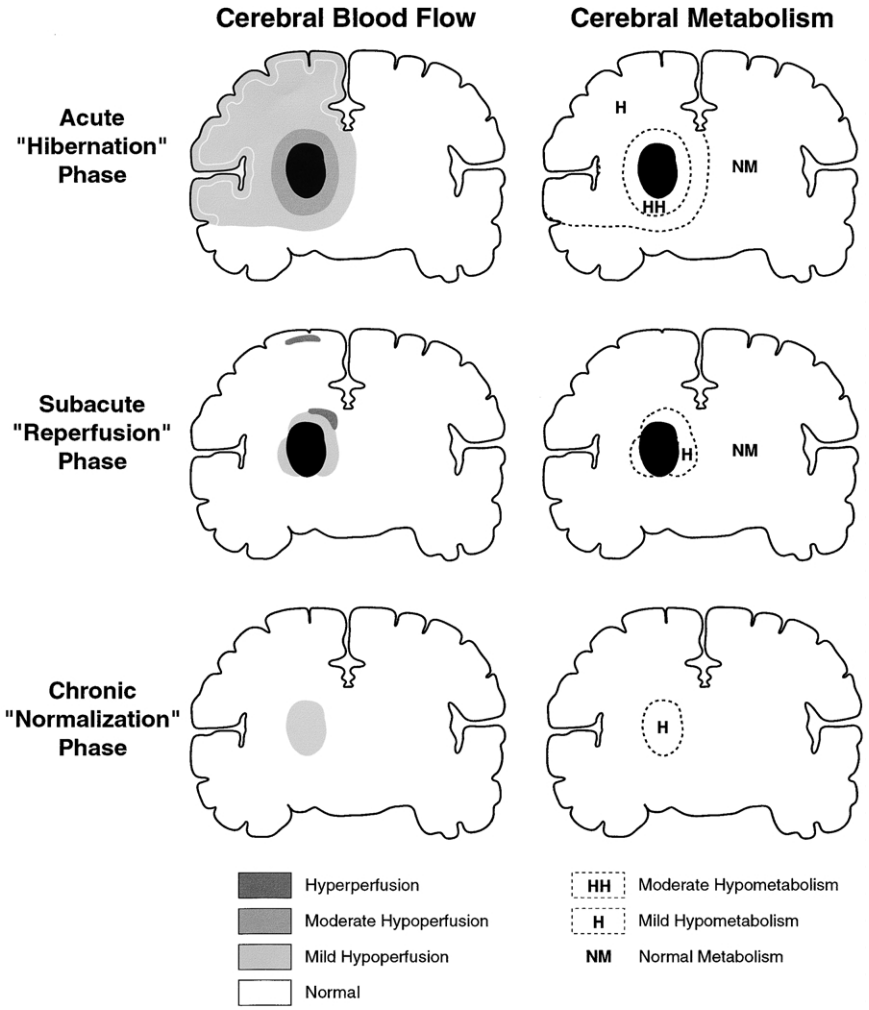

Fig. 4. Diagrammatic representation of the three phases of cerebral blood flow and metabolism changes in the acute, subacute, and chronic phases after intracerebral hemorrhage.

of hematoma expansion. Commonly, elevated blood pressure results from uncontrolled chronic hypertension and is a response to stress [33]. It can also be a protective response (referred to as the Cushing-Kocher response) to preserve cerebral perfusion, particularly in patients with evidence of brain stem compression [33]. Considerable controversy exists regarding the initial treatment of blood pressure after ICH. Most patients with ICH have chronic hypertension, which leads to cerebral autoregulation that has been adapted to higher than normal blood pressures [34]. Furthermore, CPP and autoregulatory capacity may be compromised as a result of elevated ICP [35]. Two studies have demonstrated that controlled and pharmacologically mediated reduction in blood pressure has no adverse effects on CBF in human beings or animals [22,33].

We performed a study in a canine model of ICH to determine the effect of mean arterial pressure reduction on $_{r}$CBF and ICP [33]. We tested the hypothesis that ischemia is present in the perihematoma region after ICH and that this ischemia can be exacerbated by pharmacologic reduction of mean arterial pressure. ICH was introduced in 12 anesthetized dogs by injection of autologous blood (2.8 mL in 6 animals, 4.4 mL in 6 animals) under arterial pressure in the deep white matter adjacent to the left caudate region. We obtained serial measurements of $_{r}$CBF by use of radiolabeled microspheres in the treated animals as well as in 6 control dogs. Intravenous labetalol was administered

90 minutes after introduction of either a hematoma (in treated animals) or a needle (in controls) while CPP was maintained higher than 65 mm Hg. Mean arterial pressure and ICP were monitored continuously. Elevations in ICP and mean arterial pressure were observed in the groups with ICH. These hemodynamic alterations were not accompanied by any significant differences in $_{r}$CBF. Administration of labetalol resulted in a decrease in mean arterial pressure but did not change $_{r}$CBF in the groups with ICH. In summary, pharmacologic reduction of mean arterial pressure within the normal autoregulatory limits of CPP achieved 90 minutes after introduction of the hematoma had no adverse effect on ICP and $_{r}$CBF in regions around or distant from the hematoma. These results support controlled use of antihypertensive treatment in the acute period after ICH onset.

Powers et al [22] described the changes in CBF that occur globally within the brain and regionally within the clot periphery in conjunction with pharmacologic reductions in mean arterial pressure in patients with acute ICH. Fourteen patients with acute supratentorial ICH (1–45 mL in size) were studied 6 to 22 hours after hemorrhage onset. $_{r}$CBF was measured with PET using ^{15}O-water tracer. After completion of the first CBF measurement, patients were randomized to receive either nicardipine or labetalol to reduce mean arterial pressure by 15%, and the $_{r}$CBF measurement was repeated. After administration of nicardipine or labetalol, mean arterial pressure was lowered from 143 ± 10 mm Hg to 119 ± 11 mm Hg. There was no significant change in either global CBF or pericIot $_{r}$CBF. Powers et al [22] calculated that there is less than a 5% chance of global CBF or pericIot $_{r}$CBF falling by more than -2.7 mL $\times$ 100 $g^{-1} \times min^{-1}$. They concluded that in patients with small- to medium-sized acute intracranial hematoma, autoregulation of $_{r}$CBF was preserved with arterial blood pressure reductions in the range studied.

The American Heart Association recommends that patients with ICH who present with a mean arterial pressure of greater than or equal to 130 mm Hg receive antihypertensive treatment [36]. This recommendation is based on initial evidence in animal models and human beings that supports lowering of blood pressure in the acute period of ICH. The aforementioned studies have demonstrated no unfavorable effects of controlled pharmacologic reduction of blood pressure on CBF in human beings or animal models. We do not recommend aggressive treatment of blood pressure because we have observed a poor outcome in these patients independent of other factors, including the initial Glasgow Coma Scale score and hematoma volume [37]. In most patients with chronic hypertension, cerebral autoregulation has become adapted to maintenance of higher but not lower blood pressure. Furthermore, CPP and autoregulatory capacity may be at risk for compromise to the extent that ischemia may be precipitated as a result of elevated ICP. Intravenous β-blockers and vasodilators, such as hydralazine or angiotensin-converting enzyme inhibitors, should be used for blood pressure control because they have a limited effect on arterioles in the cerebral circulation [38]. Intravenous nitroprusside or nitrates should be avoided to prevent cerebral vasodilatation and elevations in ICP. For patients with intracranial hypertension who have an ICP monitor in place, American Heart Association guidelines recommend that CPP be maintained higher than 70 mm Hg [36]. For patients with persistent hypertension, oral antihypertensives can be initiated after 72 hours of onset to gradually control blood pressure [37].

Effect of intracranial hypertension treatment on cerebral blood flow

Elevated ICP is associated with mortality after ICH [39–41]. Medical treatment of intracranial hypertension represents an important but not well-studied aspect in the management of ICH. We determined the effect of therapeutic reduction of ICP on CBF and metabolism using mannitol and hypertonic saline in a canine model of ICH [42]. We introduced ICH in three groups of anesthetized mongrel dogs, consisting of seven animals each, by autologous blood injection (5.5–7.5 mL) under arterial pressure in the deep white matter adjacent to the left basal ganglia. Iso-osmolar doses (5.5 mOsm/kg) of mannitol (1 g/kg), 3% sodium chloride (5.3 mL/kg), or 23.4% sodium chloride (0.7 mL/kg) were administered intravenously 2 hours after hematoma introduction. We then evaluated the effect of each treatment regimen on ICP, CPP, cerebral oxygen extraction, $CMRO_2$, and $_{r}$CBF in regions around and distant from the hematoma. There was an immediate reduction in ICP in each group after initiation of treatment. A gradual rise in ICP was observed in the 23.4% sodium chloride and mannitol groups with time. Only in the 3% sodium chloride group was the ICP significantly lower than the pretreat-

ment value, and this reduction occurred at 120 minutes after treatment. No significant differences were observed in $_{r}$CBF, oxygen extraction, or $CMRO_2$ at any time point (baseline; before treatment; or 15, 30, 60, or 120 minutes after treatment) among the three groups. Before treatment of modest intracranial hypertension is considered to be of no benefit, the relation between intracranial hypertension and brain damage and dysfunction should be considered. ICP is an indicator of primary injury, tissue swelling, clot volume, and ventricular dilatation, even in the presence of adequate CPP [42]. Most authors recommend treatment for ICP pressure exceeding 20 mm Hg [43,44]. In the genesis of ICP elevation resulting from brain compression caused by an expanding mass lesion, considerable increase in volume of the cranial contents may occur before spatial compensation leads to a significant rise in ICP [43,44]. Therefore, a modest rise in ICP, although not impairing $_{r}$CBF or metabolism, may be indicative of impending transtentorial herniation. The proposed benefit of intracranial hypertension treatment at this stage is to prevent subfalcine and transtentorial herniations and associated mechanical tissue damage, including brain stem compression. The risk of transtentorial herniation with consequent damage to brain stem regions is high with ICH [17,45]; in this context, early treatment may be beneficial.

In the setting of transtentorial herniation in ICH, medical treatment of intracranial hypertension may have a beneficial effect on CBF. We tested the hypothesis that transtentorial herniation represents a state of cerebral ischemia that can be reversed by the administration of hypertonic saline [46]. We produced transtentorial herniation (defined as acute dilatation of one or both pupils) by creating supratentorial ICH through the injection of autologous blood in seven mongrel dogs anesthetized with intravenous pentobarbital and fentanyl. Serial $_{r}$CBF measurements were obtained by use of radiolabeled microspheres injected in regions around and distant to the hematoma. Measurements of cerebral oxygen extraction and $CMRO_2$ were obtained by serial sampling of cerebral venous blood from the sagittal sinus. Mean arterial pressure and ICP were continuously monitored. Transtentorial herniation was successfully reversed over a mean period of 26 minutes after intravenous administration of 23.4% sodium chloride (1.4 mL/kg) in all animals. Elevation in ICP (compared with prehematoma values) was observed during transtentorial herniation with no change in CPP because of concomitant elevation in mean arterial pressure. Compared with prehematoma values, there was a significant reduction in $_{r}$CBF in the brain stem and in gray and white matter in the hemispheres ipsilateral and contralateral to the hematoma. Administration of the sodium chloride solution resulted in a reduction in ICP and a restoration of $_{r}$CBF in all regions studied, with a concomitant increase in $CMRO_2$. Compared with prehematoma values, $_{r}$CBF was found to be increased in the ipsilateral and contralateral thalamus at 15 minutes after administration of the sodium chloride solution. We conclude that transtentorial herniation represents a state of severe hypoperfusion or ischemia in the brain stem and supratentorial gray and white matter. Treatment of intracranial hypertension (using hypertonic saline) reversed transtentorial herniation and restored both $_{r}$CBF and $CMRO_2$, although hyperperfusion was observed immediately after reversal of transtentorial herniation. Rapid reversal of transtentorial herniation by aggressive treatment of intracranial hypertension may preserve neurologic function during the interim period between transtentorial herniation and surgical intervention.

Effect of hematoma evacuation on cerebral blood flow

The effect of surgical evacuation of a hematoma on CBF has been evaluated in experimental animal models and clinical studies [8,24,28,47]. Nehls et al [8] analyzed changes in CBF in an experimental model of hematoma created by inflating a balloon at the right caudate nucleus in two groups of rats. In the first group, the balloon was kept inflated for 10 minutes with subsequent deflation, simulating intraparenchymal bleeding and drainage. In the second group, the balloon was kept inflated throughout the study. Twenty-four hours after the hematomas were created, neurologic status and CBF were studied in both groups. The authors reported minor differences in CBF (determined by quantitative autoradiography) in the two hemispheres in the temporary inflation group in contrast to markedly decreased perfusion in the ipsilateral hemisphere in the group with continuous inflation. Neurologic outcome was significantly better after temporary inflation. The authors suggested that early removal of an intracerebral hematoma might have subsequent benefits in terms of CBF and outcome. Hematoma removal within 10 minutes is not feasible in the clinical setting, however, and the clinical implications

of results derived from microballoon inflation models of ICH are controversial, as previously mentioned.

Wagner et al [47] evaluated ultraearly stereotactically guided aspiration of clot after tissue plasminogen activator lysis in pigs. In one group of animals, hematomas were surgically evacuated 3.5 hours after intracerebral injection of blood, and tissue plasminogen activator was used as an adjunctive therapy to facilitate evacuation. In the second group, hematomas were not evacuated and the lytic agent was not administered. All animals received an injection of Evans blue dye 30 minutes after intraparenchymal blood infusion. The parameters (ICP, hematoma volume, perihematoma edema volume) were measured with intracranial pressure monitoring and postmortem tissue translucency studies. The investigators reported a rapid decline in elevated cerebral tissue pressure after hematoma evacuation. Analysis 24 hours later showed markedly reduced volumes of hematoma and perihematoma edema in the surgically treated group. The effect of a reduction in the rate of CBF was not studied.

Using Xe inhalation and SPECT techniques, Tanizaki [28] evaluated changes in CBF before and after stereotactic evacuation of putaminal hematomas in 13 patients. CBF improved in two thirds of patients even though all operations were performed subacutely (13–90 days from onset, mean = 30 days).

Siddique et al [24] evaluated changes in CBF measured by SPECT after ICH in a series of 13 patients. Hematomas were surgically treated in 4 patients and managed conservatively in 9 patients. These investigators defined hemisphere perfusion index as isotope count in the affected side divided by isotope count in the unaffected side multiplied by 100. The perfusion index between the first (preoperative) and second (postoperative) scans improved in all surgically treated patients. Among the conservatively managed patients, the perfusion index was worse in 6, the same in 1, and slightly better in 2.

The aforementioned studies provide early evidence that surgical evacuation of the hematoma may improve CBF. The impact of increased cerebral perfusion on clinical outcome needs to be determined.

Summary

Recent advances have furthered our understanding of changes in CBF after ICH. Recent evidence from experimental and clinical studies has not supported the role of CBF changes in the pathogenesis of neuronal injury. A better understanding of these changes in ICH has modified the basis for formulating treatment strategies and developing innovative therapies.

References

[1] Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 1993;43:461–7.

[2] Mayer SA, Lignelli A, Fink ME, Kessler DB, Thomas CE, Swarup R, et al. Perilesional blood flow and edema formation in acute intracerebral hemorrhage: a SPECT study. Stroke 1998;29: 1791–8.

[3] Nath FP, Kelly PT, Jenkins A, Mendelow AD, Graham DI, Teasdale GM. Effects of experimental intracerebral hemorrhage on blood flow, capillary permeability, and histochemistry. J Neurosurg 1987;66: 555–62.

[4] Bullock R, Brock-Utne J, van Dellen J, Blake G. Intracerebral hemorrhage in a primate model: effect on regional cerebral blood flow. Surg Neurol 1988; 29:101–7.

[5] Kingman TA, Mendelow AD, Graham DI, Teasdale GM. Experimental intracerebral mass: time-related effects on local cerebral blood flow. J Neurosurg 1987;67:732–8.

[6] Nath FP, Jenkins A, Mendelow AD, Graham DI, Teasdale GM. Early hemodynamic changes in experimental intracerebral hemorrhage. J Neurosurg 1986;65:697–703.

[7] Nehls DG, Mendelow AD, Graham DI, Sinar EJ, Teasdale GM. Experimental intracerebral hemorrhage: progression of hemodynamic changes after production of a spontaneous mass lesion. Neurosurgery 1988;23:439–44.

[8] Nehls DG, Mendelow DA, Graham DI, Teasdale GM. Experimental intracerebral hemorrhage: early removal of a spontaneous mass lesion improves late outcome. Neurosurgery 1990;27:674–82.

[9] Ropper AH, Zervas NT. Cerebral blood flow after experimental basal ganglia hemorrhage. Ann Neurol 1982;11:266–71.

[10] Sinar EJ, Mendelow AD, Graham DI, Teasdale GM. Experimental intracerebral hemorrhage: effects of a temporary mass lesion. J Neurosurg 1987;66: 568–76.

[11] Yang GY, Betz AL, Chenevert TL, Brunberg JA, Hoff JT. Experimental intracerebral hemorrhage: relationship between brain edema, blood flow, and blood-brain barrier permeability in rats. J Neurosurg 1994;81:93–102.

[12] Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28:1–5.

[13] Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27:1783–7.
[14] Qureshi AI, Wilson DA, Hanley DF, Traystman RJ. No evidence for an ischemic penumbra in massive experimental intracerebral hemorrhage. Neurology 1999;52:266–72.
[15] Wagner KR, Xi G, Hua Y, Kleinholz M, de Courten-Myers GM, Myers RE, et al. Lobar intracerebral hemorrhage model in pigs: rapid edema development in perihematomal white matter. Stroke 1996;27:490–7.
[16] Kane PJ, Cook S, Chambers IR, Mendelow AD. Cerebral oedema following intracerebral haemorrhage: the effect of the NMDA receptor antagonists MK-801 and D-CPPene. Acta Neurochir Suppl. (Wien). 1994;60:561–3.
[17] Mutlu N, Berry R, Alpers B. Massive cerebral hemorrhages. Clinical and pathological correlations. Arch Neurol 1963;8:644–61.
[18] Diringer MN, Adams RE, Dunford-Shore J, et al. Cerebral blood flow is symmetrically reduced in patients with intracerebral hemorrhage. [abstract]. Neurology 1998;50:A338.
[19] Hirano T, Read SJ, Abbott DF, Sachinidis JI, Tochon-Danguy HJ, Egan GF, et al. No evidence of hypoxic tissue on 18F-fluoromisonidazole PET after intracerebral hemorrhage. Neurology 1999;53: 2179–82.
[20] Kitahara T, Yamashita T, Kashiwagi S, Kawakami N, Ishihara H, Ito H. Hemodynamics of hypertensive putaminal hemorrhage evaluated by Xenon-enhanced computed tomography and acetazolamide test. Acta Neurol Scand Suppl 1996;166:139–43.
[21] Miyazawa N, Mitsuka S, Asahara T, Uchida M, Fukamachi A, Fukasawa I, et al. Clinical features of relative focal hyperfusion in patients with intracerebral hemorrhage detected by contrast-enhanced Xenon CT. AJNR Am J Neuroradiol 1998;19: 1741–6.
[22] Powers WJ, Zazulia AR, Videen TO, Adams RE, Yundt KD, Aiyagari V, et al. Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 2001;57: 18–24.
[23] Rousseaux M, Steinling M, Huglo D, Mazingue A, Barbaste P. Perfusion mapping with Tc-HMPAO in cerebral haematomas. J Neurol Neurosurg Psychiatry 1991;54:1040–3.
[24] Siddique MS, Fernandes HM, Arene NU, Wooldridge TD, Fenwick JD, Mendelow AD. Changes in cerebral blood flow as measured by HMPAO SPECT in patients following spontaneous intracerebral haemorrhage. Acta Neurochir Suppl. (Wien) 2000;76:517–620.
[25] Suzuki R, Ohno K, Matsushima Y, Inaba Y. Serial changes in focal hyperemia associated with hypertensive putaminal hemorrhage. Stroke 1988;19:322–5.
[26] Zazulia AR, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. J Cereb Blood Flow Metab 2001;21: 804–10.
[27] Kawakami H, Kutsuzawa T, Uemura K, Sakurai Y, Nakamura T. Regional cerebral blood flow in patients with hypertensive intracerebral hemorrhage. Stroke 1974;5:207–12.
[28] Tanizaki Y. Improvement of cerebral blood flow following stereotactic surgery in patients with putaminal haemorrhage. Acta Neurochir (Wien) 1988;90: 103–10.
[29] Carhuapoma JR, Wang PY, Beauchamp NJ, Keyl PM, Hanley DF, Barker PB. Diffusion-weighted MRI and proton MR spectroscopic imaging in the study of secondary neuronal injury after intracerebral hemorrhage. Stroke 2000;31:726–32.
[30] Kidwell CS, Saver JL, Mattiello J, Warach S, Liebeskind DS, Starkman S, et al. Diffusion-perfusion MR evaluation of perihematomal injury in hyperacute intracerebral hemorrhage. Neurology 2001;57:1611–7.
[31] Uemura K, Shishido F, Higano S, Inugami A, Kanno I, Takahashi K, et al. Positron emission tomography in patients with a primary intracerebral hematoma. Acta Radiol Suppl 1986;369:426–8.
[32] Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. Stroke 1997;28:1396–400.
[33] Qureshi AI, Wilson DA, Hanley DF, Traystman RJ. Pharmacologic reduction of mean arterial pressure does not adversely affect regional cerebral blood flow and intracranial pressure in experimental intracerebral hemorrhage. Crit Care Med 1999;27: 965–71.
[34] Heistad DD, Mayhan WG, Coyle P, Baumbach GL. Impaired dilatation of cerebral arterioles in chronic hypertension. Blood Vessels 1990;27:258–62.
[35] Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A. Dysautoregulation in patients with hypertensive intracerebral hemorrhage. A SPECT study. Neurosurg Rev 1995;18:237–45.
[36] Broderick JP, Adams HP, Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council. American Heart Association. Stroke 1999;30:905–15.
[37] Qureshi AI, Bliwise DL, Bliwise NG, Akbar MS, Uzen G, Frankel MR. Rate of 24-hour blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. Crit Care Med 1999;27:480–5.
[38] Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med 2001;344:1450–60.

[39] Janny P, Colnet G, Georget AM, Chazal J. Intracranial pressure with intracerebral hemorrhages. Surg Neurol 1978;10:371–5.
[40] Papo I, Janny P, Caruselli G, Colnet G, Luongo A. Intracranial pressure time course in primary intracerebral hemorrhage. Neurosurgery 1979;4:504–11.
[41] Ropper AH, King RB. Intracranial pressure monitoring in comatose patients with cerebral hemorrhage. Arch Neurol 1984;41:725–8.
[42] Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. Neurosurgery 1999;44:1055–64.
[43] Diringer MN. Intracerebral hemorrhage: pathophysiology and management. Crit Care Med 1993; 21:1591–603.
[44] Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ. Significance of intracranial hypertension in severe head injury. J Neurosurg 1977;47:503–16.
[45] Stober T, Sen S, Anstatt T, Bette L. Correlation of cardiac arrhythmias with brainstem compression in patients with intracerebral hemorrhage. Stroke 1988;19:688–92.
[46] Qureshi AI, Wilson DA, Traystman RJ. Treatment of transtentorial herniation unresponsive to hyperventilation using hypertonic saline in dogs: effect on cerebral blood flow and metabolism. J Neurosurg Anesthesiol 2002;14:22–30.
[47] Wagner KR, Xi G, Hua Y, Zuccarello M, de Courten-Myers GM, Broderick JP, et al. Ultra-early clot aspiration after lysis with tissue plasminogen activator in a porcine model of intracerebral hemorrhage: edema reduction and blood-brain barrier protection. J Neurosurg 1999;90: 491–8.